EXHIBIT 31

REMARKS

Applicants hereby request further consideration of the application in light of the following remarks.

I. STATUS OF THE APPLICATION

Claims 34, and 72-78 stand rejected as obvious in view of Deboeck ('628), Stamm ('670) and Department of Health and Human Services, FDA CDER, Oct. 1997 ("HHS"). Applicants traverse the rejection.

II. APPLICANTS' SUMMARY OF INTERVIEW

Applicants gratefully acknowledge the in-person interview conducted on October 2, 2007 with Examiner Gembeh and Supervisory Examiner Marsch. The interview substantially advanced prosecution, and expedited disposition of the application.

The various rejections and references relied upon were discussed. Applicants showed that Deboeck and Stamm are non-analogous art. As explained in more detail below, Deboeck is directed to a melt of fenofibrate and excipients poured into capsules. Deboeck teaches away from micronized fenofibrate formulations. Stamm is directed to micronized fenofibrate formulations, but does not teach or suggest the claimed quantities of binding cellulose derivative. Moreover, neither reference achieves the reduction in food effect achieved by applicants' pharmaceutical compositions. Accordingly, Applicants showed that the rejection failed to make a *prima facie* case of obviousness.

III. THE CLAIMED INVENTION

The claimed invention is a method for reducing food effect when treating hypertriglyceridemias, hypercholesterolemias, and hyperlipidemias. The method involves administering to patients a pharmaceutical composition comprising granules of neutral cores coated with an active layer of micronized fenofibrate, a surfactant and a binding cellulose derivative. The quantity of binding cellulose derivative is between 2 and 15 % by weight of the composition.

Neutral cores are well known and widely used within the pharmaceutical arts, and are generally understood to be about 200 to about 1000 microns in diameter. The resulting granules, or coated neutral cores, are compounded for administration, e.g., in a capsule. It will be understood that each capsule would comprise a great many discrete and individual granules.

By way of illustration, the granules can be envisioned as a sphere such as an orange wherein the fruit is the neutral core and the rind is the active layer. As such, the granules are carefully constructed as an integrated whole having controlled and somewhat uniform concentrations of the various constituents.

The granules of the present invention are organized structures having specific physicochemical relationship between the neutral core, the active agent, and binding cellulose derivative. The claimed granules are distinct from formulations having similar ingredients but lacking organized structure or fixed interrelationship, e.g., mixtures of solid fenofibrate powder and capsule-filling excipient powders such as lactose, starch etc. (See, e.g., EP 0330532, cited at Deboeck, col. 1, lines 46-61); or wherein the various ingredients are combined in an amorphous melt or suspension, as in Deboeck itself.

The claims remain as presented in the previous Response but with the addition of new claim 79. The new claim is similar to claim 34, but recites that the weight of the binding cellulose derivative is 2-15% of the weight *of the granules*. This is different from claim 34's recitation of the cellulose derivative as a percentage of the composition, and is introduced in contemplation of the use of the granules in a pharmaceutical formulation with other active agents.

IV. PRIOR ART REJECTIONS

The rejection fails to make a *prima facie* case, and thus should be withdrawn in favor of a Notice of Allowance as to all pending claims.

Deboeck fails to teach or suggest the claimed invention, either alone or in combination with the subsidiary references. The claimed invention is distinguishable over Deboeck in that the present claims expressly require micronized fenofibrate. Deboeck itself expressly distinguishes its formulations from those involving micronization.

A. DEBOECK TEACHES AWAY FROM MICRONIZATION

Deboeck describes pharmaceutical formulations for treatment of hypercholesterolemia and/or hyperlipidemia. Col. 1, l. 13-16 and Col. 2, l. 31-33. Deboeck's stated objective is to "provide a fenofibrate formation not requiring use of co-micronization which, nevertheless, exhibits a bioavailability comparable to formulations of fenofibrate which do." Col. 2, l. 12-15. As an alternative to micronization, Deboeck recommends forming a melt of fenofibrate and excipients including one or more polyglycolized glycerides. Col. 2, l. 31-37. The fenofibrate is

soluble in the excipients. Col. 2, l. 38-43. The resulting homogeneous fenofibrate melt solution is used to fill hard gelatin capsules. Col. 2, l. 55-60.

B. DEBOECK FORMS A MELT THAT AVOIDS FORMATION OF FENOFIBRATE CRYSTALS

Deboeck states that its melt formulations can be made without regard to particle size specifications. Col. 2, l. 38-43. Indeed, Deboeck state that addition of a suspension stabilizer to the molten solution of fenofibrate *avoids the formation of fenofibrate crystals* during the cooling of the filled hard gelatin capsules. Col. 2, l. 44-48. The formulations are said to require fewer steps and are therefore more advantageous than micronization of powders. Col. 2, l. 65-67.

Deboeck states that methods requiring micronization are more costly, and offers as an advantage of its method that it eliminates the need for such a costly process. Further, as Deboeck forms a melt, one would have recognized that any benefits associated with micronization would be lost and the added cost would not be justified. One skilled in the art would understand from Deboeck's characterization that its formulations are incompatible with micronization; or, at the very least, that micronization would add cost without advantage. Thus, there would have been no motivation to use a micronized fenofibrate with the Deboeck formulations and methods.

Moreover, the micronized fenofibrate of the presently claimed invention must be incorporated in a pharmaceutical formulation wherein the micronized fenofibrate is part of an active layer coated on neutral cores. The Deboeck reference describes a formulation wherein the non-micronized fenofibrate is a melt used to fill a gelatin capsule. The rejection cites no teaching or suggestion that one might incorporate

neutral cores. And even if one were to incorporate such neutral cores, the fenofibrate of Deboeck is, as stated above, not micronized.

C. DEBOECK'S FORMULATIONS EXHIBIT A PRONOUNCED FOOD EFFECT

The rejection asserts that Table 4 of Deboeck "teaches the bioavailability of fenofibrate is equivalent to when the patient has fasted." Applicants respectfully disagree. Table 4 shows that the bioavailability of Deboeck's formulation differs substantially as between the fed and fasted state. This is supported by the methodology of the HHS reference, which is relied upon as a prior art reference in the rejection.

The HHS reference addresses "Food-Effect Bioavailability and Bioequivalence Studies." Among other things, it acknowledges and identifies the food effect and its various causes, particularly as it relates to bioavailability and bioequivalence. It describes accepted methodology for determining whether the food effect is absent, or whether it is documented (confirmed). According to that methodology, Table 4 confirms that Deboeck's formulation (Example 2) demonstrates a profound food effect.

The HHS reference states that the food effect is documented (confirmed) when the ratio of fed to fasted treatments falls outside 80-125% AUC and outside 70-143% C_{max}. HHS, p. 6. In Deboeck's Example 2, the fed to fasted ratio is 169% AUC and 217% C_{max}. Thus, Table 4 confirms that the Deboeck formulation suffers from a significant food effect.

In contrast, the fed to fasted ratio of the presently claimed invention is substantially lower than Deboeck's formulation. Indeed, by at least one measure, the

ratio is within the range specified by the HHS as showing no food effect (i.e., AUC fed/fasted is 124%, Specification, Table 2, page 24), which represents a significant reduction as compared to the cited art, and thus demonstrates a surprising and unexpected result.

D. DEBOECK'S CELLULOSE DERIVATIVES SERVE A DIFFERENT PURPOSE

Further, Deboeck's filling method involves forming a melt. Col. 2, l. 38-43. According to Deboeck, the melt benefits from the addition of a suspension stabilizer. Deboeck's exemplary stabilizers are cellulose derivatives, e.g., hydroxypropylmethyl cellulose (HPMC) or hydroxypropyl cellulose (HPC). However, the only motivation Deboeck provides for adding cellulose derivatives is as a suspension stabilizer. In the absence of a melt or suspension, one of ordinary skill in the art would have found within Deboeck no motivation to add such a stabilizer. As the presently claimed invention does not involve the formation of a melt or suspension, Deboeck affords no teaching or suggestion to incorporate a stabilizer. Thus, there is no suggestion within Deboeck to add such a cellulose derivative.

E. STAMM'S FORMULATIONS ARE MICRONIZED

The shortcomings of Deboeck are not remedied by the secondary references. Stamm ('067), unlike Deboeck, relates to a micronized fenofibrate formulation. Thus, one of ordinary skill in the art would not have been motivated to look to Stamm to overcome Deboeck's shortcomings, whatever they might have been. Indeed, the rejection fails to identify any acknowledged shortcoming in Deboeck that would have motivated anyone to go beyond that reference, much less to look specifically to

Stamm. Even if one had gone beyond Deboeck, it is unlikely that they would have combined the teaching of Deboeck with Stamm as the two references deal with fundamentally different formulations (e.g., melt v. micronized).

Even if one were to combine those references, there is no showing that such a combination would have led one to the claimed invention. There is nothing in the two references suggesting that any such combination could produce a pharmaceutical formulation having the pronounced reduction in food effect as is shown in Applicants' Table 2.

F. STAMM DOES NOT SUGGEST THE CLAIMED RATIO OF CELLULOSE DERIVATIVE

As acknowledged in the Official Action, Stamm does not teach or suggest the presently claimed ratio of a binding cellulose derivative. Stamm refers to a hydrophilic polymer, and some of those are cellulose derivatives. The rejection asserts that ingredient could be readily optimized. Applicants disagree.

1. Stamm & Deboeck Use Cellulose Derivative for Different Purposes & So There is No Suggestion as to Why or How to Optimize

The rejection fails to show how or why one might modify that ingredient. Optimization for Stamm's purpose does not equal optimization here, nor would it result in optimization in Deboeck. In Deboeck, it is a suspension stabilizer. There is simply no need for a suspension stabilizer here. According to Deboeck then, an optimized amount would be zero in the presently claimed formulation. To the extent that there is an analogous ratio in Deboeck, it would have no relevance here as there

would be no well-reasoned basis for adding any suspension stabilizer to a formulation not involving a suspension.

2. Stamm Does Not Suggest Modifying Hydrophilic Polymer

Further, the rejection fails to show that anything within Stamm teaches or suggests that the hydrophilic polymer is a result-altering variable, particularly as it relates to food effect.

Even if a person of ordinary skill in the art were to combine the Deboeck and Stamm references, and if that person were to select the various and disparate ingredients, and the appropriate form of those ingredients, so as to arrive at the present invention, there is no suggestion that such person would have modified the quantities of those ingredients such that they would have arrived at the presently claimed invention.

G. HHS DOES NOT SUGGEST HOW TO ELIMINATE FOOD EFFECT

Nor does the HHS reference remedy the deficiencies of the combination of Deboeck and Stamm. First, the HHS reference is entirely silent as to any of the mentioned ingredients of the claimed formulations, and thus fails to provide any guidance as to how the various ingredients might be formulated and combined to arrive at the claimed invention. Second, the HHS reference does not suggest how any of those ingredients might be modified or quantities adjusted to reduce the food effect. Rather, the HHS reference acknowledges that there is a food effect on certain active agents and formulations, and describes recommendations for measuring it, not eliminating it.

Further, the reference is silent as to whether there is a food effect with fenofibrate, and, as such, does not teach or suggest how to eliminate it. Thus, the HHS reference does not suggest the claimed method for reducing food effect in a fenofibrate formulation. The HHS reference fails to provide any additional teaching or suggestion that would have led one of ordinary skill in the art from the Deboeck or Stamm references to the claimed invention.

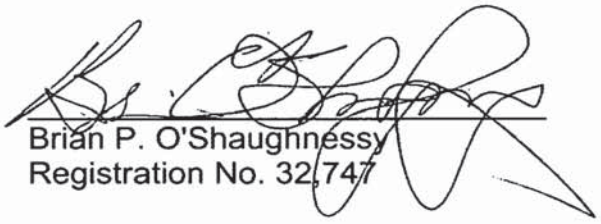
H. CONCLUSION

Applicants submit that the claims are now in condition for allowance, and request formal notification to that effect. If, however, the Examiner perceives any impediments to such notification, whether formal or substantive, Applicants encourage the Examiner to contact their representative. Such communication will expedite examination and disposal of the application.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: October 26, 2007

By: 

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